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Original research

Total thyroidectomy with harmonic scalpel combined to gelatin-thrombin matrix hemostatic agent: Is it safe and effective? A single-center prospective study

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ABSTRACT

Introduction: Hemostasis during thyroidectomy is essential; however, the safest, most efficient and cost-effective way to achieve this is unclear. The aim of this study was to evaluate the outcome of total thyroidectomy (TT) performed with combination of harmonic scalpel (HS) and Floseal.
Methods: Patients undergone TT were divided into two groups: HS + Floseal and traditional hemostasis groups. The primary endpoint was 24-h drain output and blood-loss requiring reintervention. Secondary endpoints included surgery duration, postsurgical complications and hypocalcemia rates.
Results: Between September 2012 and January 2014, 165 patients were enrolled (100 to HS + Floseal, 65 to standard hemostasis); 80.5% female; mean age 42.3 years. The 24-h drain output was lower in the HS + Floseal group compared with standard TT. HS + Floseal also had a shorter mean surgery time ($p < 0.0001$) vs standard TT. No differences in post-surgical complications and in hypocalcemiarates between groups.
Conclusion: combination of Floseal plus the HS is effective and safe for TT and it provides a complementary hemostatic approach.

1. Introduction

Total thyroidectomy (TT) is the preferred option for the management of benign multinodular goiter and the standard treatment for cancer [1–4]. An accurate dissection and hemostasis is essential in order to provide a clear surgical field during TT, minimize the risk of structural damage, prevent post-surgical hemorrhage and avoid the need for surgical drains; however, the safest, most efficient and cost-effective way to achieve these goals is still under debate. Besides the traditional surgical hemostatic techniques, different hemostatic approaches which further minimize the risk of bleeding and complications during thyroidectomy have become available. These include ultrasonic coagulation, bipolar coagulation and modern topical hemostatic agents.

The Harmonic Scalpel (HS), a device that uses ultrasonic coagulation via high frequency mechanical vibration (in the range 55,500 Hz) to allow both a cutting and hemostatic effect simultaneously [5], has been shown to be an effective surgical device which decreases operative time, complications and bleeding in a variety of surgical procedures [6–14]. The hemostatic effect is achieved via protein denaturation rather than heat used in electrosurgical hemostatic devices, which uses a high electric current to produce the heat required for the hemostatic effect [15].

Floseal Hemostatic Matrix (Floseal; Baxter Healthcare Corporation, USA), a gelatin-thrombin matrix topical hemostatic agent that has been on the market in the US and in Europe since 1999 [16], is a combination of bovine-derived cross-linked gelatin granules and topical human thrombin. It has been proven to reduce blood loss in a variety of surgical procedures [17–26] including thyroid surgery [27].

The aim of this study was to evaluate the outcome of these two hemostatic approaches in combination, with their different and potentially complementary mechanisms, in patients undergoing TT.

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2. Methods

2.1. Study design

This single-center, prospective study investigated the hemostasis efficacy and safety of Floseal + HS (Harmonic Focus; Ethicon Endo-Surgery, Norderstedt, Germany)in patients undergoing TT. Two groups were assessed: patients receiving Floseal + HS, and patients receiving traditional hemostatic procedures alone (gauze, ligature, electrocauterization) during TT.

The protocol was reviewed and approved by local Independent Ethics Committee/Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki and according to local and regional ethical standards. Written informed consent was obtained from all patients.

2.2. Patients

Patients were included if they were ≥18–70 years of age and were planning to undergo total thyroidectomy due to thyroid disease. Patients were excluded from the study if they had diabetes, chronic renal disease or other metabolic diseases, had received previous neck irradiation or surgery, had cervico-mediastinal goiters, required lymphadenectomy, had a planned video assisted thyroidectomy (minimally invasive) or one lobe pathology where only hemi-thyroidectomy was planned, had known coagulopathy, had active or past history of malignant systemic disease, were pregnant or lactating females, had a known allergy to the components of Floseal, were known to abuse drug or alcohol, or were receiving chronic cortisone or platelet inhibitors.

2.3. Treatments and surgical technique

Total thyroidectomy was performed using institutional guidelines by experienced surgeons [28,29]. A 4–6 cm Kocher incision was made at the lower neck crease two fingers above the suprasternal notch with a scalpel. Traditional hemostatic procedure was performed as follows: after division of the platysma, the cervical linea alba is opened without division of the strap muscles. The thyroid lobe is dissected progressively from the strap muscles. Thyroid vessels were ligated and divided, rotating the thyroid lobe medially before dividing vessels in the ligament of Berry, supervising and saving the recurrent laryngeal nerve, and the thyroid lobe is removed. The procedure was repeated for the contra lateral lobe. After a check for hemostasis, a drain is placed in the thyroid bed. The cervical linea alba and platysma are sutured with absorbable sutures, and the skin is closed by an intracutaneous running suture.

In patients undergoing TT with HS + Floseal, dissection and ligation of vascular pedicles was done using the HS, with surgical hemostasis used if additional hemostasis was deemed necessary and Floseal was used for bleeding not responding to surgical hemostasis, in particular in the Gruber and Sappey ligaments, avoiding electrocautery injuries to recurrent nerves.

In all patients a suction surgical drain was placed for the first 24 h, as part of this study, in order to better objectivize and quantify blood loss, although some centers did not longer consider drainage useful after thyroidectomy.

All patients received the same postoperative protocol. Surgical drain was removed after 24 h; a neck ultrasonographic evaluation was performed 48 h after surgery to verify the presence of seroma or blood collections. All patients in the study were discharged on postoperative day 3 (72 h after surgery) for better evaluation of the postoperative course. The postoperative follow-up care included indirect laryngoscopy to check vocal cord mobility. An indirect laryngoscopy was performed on postoperative day 2 to assess transitional or permanent paralysis of laryngeal nerve; in case of incidence of dysphonic voice, laryngoscopy was also reconsidered after 1 week and 3 months.

The serum calcium level also was measured for all patients at 6, 12, 24, 48 h. In case of symptomatic hypocalcemia, intravenous calcium was administered; in asymptomatic hypocalcemic patient, oral calcium was given.

2.4. Study endpoints

The primary endpoint was the drain output (ml) after 24 hours and the presence of a significant blood loss (if patient needed to return to OR). Secondary endpoints included presence of seroma, the duration of surgery, post-surgical complications and post-surgical serum calcium level.

2.5. Statistical analysis

Qualitative and quantitative descriptive analyses were performed for all the variables collected. Qualitative variables were analyzed using frequencies and percentages. Quantitative variables were studied through the mean, standard deviation (SD), median and interquartile (IQR) range (25 percentile – 75 percentile). Parametric (analysis of variance [ANOVA]) and nonparametric tests (Wilcoxon) were used for comparisons of numerical variables. For the primary endpoint a Bonferroni adjustment was performed to account for multiplicity. Fisher's exact test was used for comparison of categorical variables. In all statistical hypotheses, the significance level was set at $\alpha = 0.05$. All analyses were performed with the SPSS software version 17.0.

3. Results

3.1. Baseline characteristics and patient disposition

Between September 2012 and January 2014, 165 patients were enrolled (100 to HS + Floseal, 65 to standard hemostasis). Of the 165 patients, 80.5% were female and the mean age was 42.3years.There were no meaningful differences between the two treatment groups with respect to demographic or baseline characteristics (Table 1). However, the type of thyroid disease in each group varied slightly between the treatment groups.

Table 1
Baseline characteristics/demographics and surgical parameters.

Characteristic/demographic	HS + Floseal TT ($n = 100$)	Standard TT ($n = 65$)
Mean age, years	49.3 ± 12.2	48.7 ± 12.2
Range	30.1–71.8	23.2–69.4
Gender, *n* (%)		
Male	28 (28)	15 (23)
Female	72 (72)	50 (77)
BMI, kg/m^2	23.7 ± 2.8	23.4 ± 3.3
Pulse rate, bpm	73.0 ± 6.89	73.6 ± 7.75
BP, mmHg		
Systolic	123.7 ± 10.7	125.0 ± 12.4
Diastolic	77.9 ± 6.6	78.8 ± 6.2
Thyroid disease, *n* (%)		
Goiter	79 (79)	48 (73.9)
Hyperthyroid goiter	9 (9)	7 (10.7)
Carcinoma	12 (12)	10 (15.4)
Thyroid weight, g	32.8 ± 3.3	45.9 ± 27.3

All data is presented as mean ± standard deviation (SD) unless otherwise stated. BMI, body mass index; BP, blood pressure; bpm, beats per minute; CS, clinically significant; ECG, electrocardiogram; HS, harmonic scalpel.

3.2. Surgical outcome

Surgery was uneventful in the majority of patients (Table 1). Three patients standard TT had surgical complications, with one patient having dystonia with a saturated O_2 of 98%.Compared with HS + Floseal, fewer patients who received standard hemostasis during surgery had a dry surgical field at the end of surgery and before placement of the drain according to the surgeon (100% vs 85.6%, $p < 0.001$). No other meaningful differences between the two treatment groups with respect to surgery were reported.

3.3. Efficacy outcomes

Drain output over 24 h was significantly lower in patients who received during surgery .The mean of 24-h drain output was 48.1 ± 20.4 mL in HS + Floseal group vs 97.9 ± 24.2 mL in standard TTgroup (95% CI − 63.5, −32.3; $p < 0.0001$) (Table 2).

Incidence of post-operative seroma was higher in standard hemostasis group.

There was a statistically difference in the length of surgery: patients in the HS + Floseal group had a shorter mean surgery time, compared with standard hemostasis ($p < 0.0001$) (Table 2).

Only one patient in standard hemostasis group developed temporary laryngeal nerve paralysis; however, this condition resolved at the 3-month follow-up visit. Another patient who received HS + Floseal and one patient in standard hemostasis group developed hypomobility of the right side. Again this was resolved at the 3-month follow-up.

No significant differences in the rates of hypocalcaemia (serum calcium <8.0 mg/dL) were observed between treatment groups ($p = 0.37$). Laboratory hypocalcaemia was reported in 17.6% and 22.7% of patients in the HS + Floseal and standard hemostasis groups, respectively. Similar results for the rate of symptomatic hypocalcaemia was also observed ($p = 0.52$).

4. Discussion

To our knowledge this is the first study to investigate the hemostasis efficacy and safety of HS + Floseal in patients undergoing TT. This study showed that the use of HS + Floseal can reduce drain output compared with the standard TT, avoiding post-operative seroma incidence. Our results are similar to those investigating Floseal + HS in patients undergoing thyroidectomy or laparoscopic transperitoneal partial nephrectomy [20]. Similarly, other studies on patients undergoing thyroidectomy [8,30]or laparoscopic transperitoneal partial nephrectomy show all procedures were feasible, safe, successful and reproducible by surgeons used to complex laparoscopic procedure.

In our study the latter model of HS, the Harmonic Focus, was used. It has been shown that this device can reduce mean operative time in a prospective randomized study that compared outcomes using two models of HS: the Harmonic Focus ($n = 45$) and the older Harmonic Ace ($n = 45$) in patients undergoing thyroid surgery [31]. We found similar data regarding operative time, showing a reduction in the duration of surgery, allowing a shorter anesthesia and a possibility to save time for other surgery in a single center.

All of the surgeons who performed TT in this study were considered experts, with over 100 previous thyroidectomies conducted. The effect of a surgeons previous experience had been investigated in a retrospective analysis which considered the effect of the 'learning curve' in the use of the HS, by comparing outcomes after total thyroidectomy in the 12 months prior to adoption of the HS (2003; $n = 77$) and in a period of12 months, 2 years after the HS was adopted (2006; $n = 106$). Results showed that, once past the learning curve, the HS significantly reduces operative time and postoperative hypocalcaemia, and is as safe as conventional surgery with regard to voice change and bleeding [32].These individual studies showing benefits with the HS are further supported by three meta-analyses [9,33,34].

Cost-effectiveness of the HS over traditional methods has also been demonstrated in an analysis of data from a randomized controlled trial of 198 patients undergoing surgery with the ultrasound scalpel ($n = 96$) or traditional surgical methods ($n = 102$) using a hospital, third party payer and societal perspectives [35]. The HS provided a shorter mean operation time ($p < 0.001$) and greater improvements in quality of life ($p = 0.002$) versus traditional methods and cost effectiveness was demonstrated from a hospital perspective (saving €119/patient) and a societal perspective (lower medical and non-medical resource consumption during the 3 months post discharge follow-up period), calculated as an overall saving of €325.36/patient [35].

In our study, incidence of post-operative complications was low in both groups, in particular for vocal cord palsy. Our findings are in agreement with those reported in previous similar studies. The lack of post-surgical complications including nerve injuries at the 3 months' follow-up in any groups was expected due to the high level of surgical expertise. However, substituting electric coagulation near Gruber ligament with hemostasis provided by Floseal, could lower incidence of accidental recurrent nerve lesions [36–39].

There were also no significant differences between treatment groups in the rate of hypocalcaemia. However, the rate was lower in the HS + Floseal group versus standard TT (17.6% vs 22.7%, respectively). This little difference can be explained by a diminished parathyroid gland "stupor" from electrical spread using HS + Floseal. There were no unexpected results from this study and our findings were compatible with recent Literature [40–42].

Table 2
Secondary endpoints.

Outcome	HS + Floseal TT ($n = 100$)	Standard TT ($n = 65$)
Drain output over 24 h, mL		
Mean ± SD	48.1 ± 20.4	97.9 ± 24.2*
Length of surgery, min		
Mean ± SD	53.97 ± 15.26	88.67 ± 26.27*
Hospital stay, days		
Mean ± SD	2.46 ± 0.59	2.59 ± 0.57

*$p < 0.001$.
HS, harmonic scalpel; SD, standard deviation.

5. Conclusions

This study shows that using a combination of Floseal plus the HS is effective and safe for TT. Mean surgery time can be reduced as well as 24-h post-surgical drain output and seroma formation, without any increased risk of post-surgical complications. We believe that Floseal Hemostatic Matrix plus the HS could provide a complementary hemostatic approach in patients undergoing total thyroidectomy. Further research is required to investigate the cost-effectiveness of this combined approach in patients undergoing thyroidectomy compared with convention and other approaches.

Ethical approval

Local Board approved the study.

Conflicts of interest

Authors declare no conflict of interest related to the subject of this study.

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None.

Author contribution

Giovanni Docimo: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript and gave final approval.

Salvatore Tolone: Participated substantially in conception and design of the study.

Roberto Ruggiero: Participated substantially in the drafting and editing of the manuscript.

Gianmattia del Genio: Participated substantially in the drafting and editing of the manuscript.

Luigi Brusciano: Participated substantially in collecting data.

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Alfonso Bosco: Participated substantially in collecting data.

Domenico Parmeggiani: Participated substantially in collecting data.

Cosma Cosenza: Participated substantially in collecting data.

Paolo Limongelli: Participated substantially in the analysis and interpretation of data.

Ludovico Docimo: Gave final approval.

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